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Using Simple Fluid Wetting as a Model for Cell Spreading

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Cell morphology in contact with external media is dictated by the cell's interactions with the external media. One component that influences morphology is the thermodynamic aspect of cell spreading, which can be seen as analogous to wetting in a three-phase equilibrium. Results of classical density functional theory within the mean field approximation for a binary fluid are summarized to motivate simple changes to the model through the effective mass coefficient. We find that by altering the effective interactions we can alter the stable morphology, increasing contact by increasing component similarity. Thus we are able to propose a systematic approach to modeling cell spreading from simple mean field results.

1 Background

The spreading of a cell on a surface, though complex, is driven primarily by two components. One is a mechanical force from actin filament formation. The other is a more thermodynamic driving force, associated with balancing surface interactions, that allows analogy to simple wetting phenomena. This influence is visible in cell-cell contacts, such as found in tissues, and is of particular importance in biomedical applications[1], where patterned substrates are often employed in the design of biomimetic materials[2]. The rate and extent of adsorption depends on the surface film's composition[3,4], which is exploited in micro-patterning applications[5].

To develop the thermodynamic basis for cellular spreading from a line of three-phase contact, the cell-substrate-surround system can be envisioned as a constrained three-phase equilibrium, where there are two true phases and a third (the cell) which mimics one. Viewed in such a manner, there is readily conceivable an analog to the line tension which behaves characteristically in the spreading process, as is the case for a drop on a surface.

There are three general morphologies available to a drop in contact with an interface, shown in Figure 1. These are determined by the balance of interactions between the phases and characterized by a contact angle determined directly via Young's Law[6]. The drop can "bead" (Fig. 1(a)) or spread only minimally (non-wetting), as the system attempts to minimize the unfavorable interactions between the phases. Alternatively, it can spread unrestrictedly across the surface and wet it completely (Fig. 1(c)). Between these two regimes there is an intermediate state, in which the drop only partially wets the surface (Fig. 1(b)). In these instances, there is a line of three-phase contact along the drop boundary. Immediately before complete wetting, there is another possibility, that of pre-wetting (Fig. 1(d)), in which a layer of finite thickness first coats the interface before a discontinuous transition to infinite thickness occurs. Because the extent of cellular spreading is bounded by the cell membrane, it is to this final possibility that comparisons are most natural.

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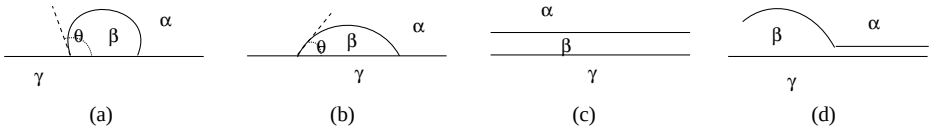


Figure 1. Wetting states possible for a drop on a surface: (a) non-wetting; (b) partial wetting; (c) complete wetting; (d) pre-wetting.

2 Simple Fluid wetting in a binary system

A binary three-phase system consists of two components ($i = 1, 2$) in three phases (α, β, γ), all of which are in equilibrium with each other, as shown in Figure 2, and is described by a free energy functional dependent upon the spatial component densities, $F[\rho_1, \rho_2]$. At the intersection of the three two-phase boundaries ($I = \alpha\beta, \beta\gamma, \alpha\gamma$), there is a line where all three phases are in contact. About this boundary there is a two-dimensional region of inhomogeneities which gives rise to an excess concentration along the line of three-phase contact. This results in an excess contribution to the free energy, yielding the line tension.

A commonly assumed model free energy density, Ψ, accounts for the variation of the densities in the region of the phase interfaces to second order:

$$\Psi = F[\rho_1, \rho_2] + \frac{1}{2}\sum_{i,j} m_{ij} \nabla\rho_i \cdot \nabla\rho_j, \tag{1}$$

where m_{ij} is a constant mass interaction term. The surface tension, σ_I, is determined by integrating this excess across the interface. The overall excess free energy is found similarly, and the surface excesses subtracted to yield the line tension:

$$\tau = \min_{\rho} \left[\int_A \Psi[\rho_1, \rho_2] da - \sum_I (\sigma_I R_I) \right] = \int_A (\Psi[\rho_1, \rho_2] - 2F[\rho_1, \rho_2])\, da. \tag{2}$$

The latter form of the line tension, due to Kerins and Boiteux[7], converges to the preceding variational form. Solving the Euler-Lagrange equations subject to the bulk conditions is

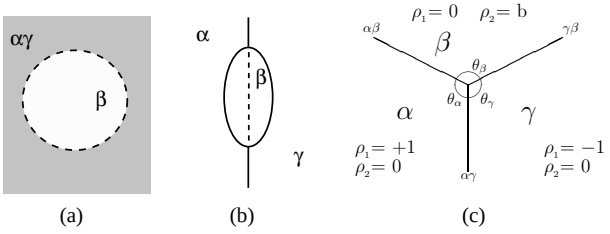
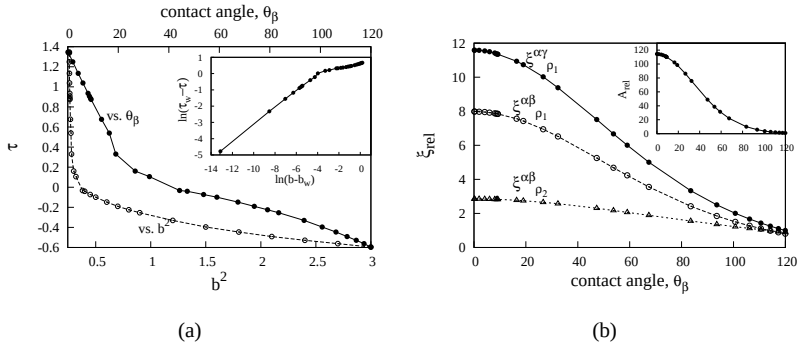


Figure 2. Model system for a drop of phase β at the interface between phases α and γ. (a): Top view of the drop showing the three-phase contact (dashed line); (b): Side view of the drop on the interface; (c): Region normal to the line of three-phase contact, showing the bulk component densities in each of the phases.



(a) (b)

Figure 3. Results of solving the model binary system. (a) Line tension approaching wetting; (b) Response of the contact regions approaching the transition, relative to the $b = \sqrt{3}$ values. Used by permission from Ref.[9].

equivalent to minimizing the the free energy per unit area and yields the equilibrium density profiles without restricting them to a particular form.

The model system studied previously by Taylor and Widom[8,9] is shown in Figure 2(c). It is described by a model free energy functional, $F\left[\rho_1, \rho_2; b\right]$[10], which depends upon the relative component densities and a parameter (b, the bulk density of one of the components) which can be varied to induce a wetting transition, and $m_{ij} = \delta_{ij}$.

The line tension and contact region in this model exhibit an interesting behavior approaching the wetting transition, both changing qualitatively at the same point. In the line tension, shown in Figure 3(a), the slope changes near 20°. A shift between clearly different structures occurs in the that region ($b^2 \sim 0.3$, $\theta_\beta \sim 20^\circ$), resulting in an average behavior which satisfies the mean field prediction. The spatial extent of the inhomogeneous region of the phase contact (measured by the correlation length ξ), Figure 3(b), supports this, exhibiting a distinct plateau in the growth rate of the contact area at the same region.

Thus in even a so simple model there is non-uniformity, and it is this observation which motivates our current work, as it facilitates extension to systems where such behavior is involved. Such an approach allows the model to be applied to more complex systems by incorporating simple modifications.

3 Extending the model

The simple picture above is modified by altering the balance of the components within the square-gradient approximation, by scaling the off-diagonal values of the effective mass interaction parameter, m_{ij}. The rest of the model is as in the work of Taylor and Widom[9].

A first test employs a value of $m_{12} = 0.75$ and maintains the self-interaction constant at unity. In this manner, the components are made to appear more similar, and the static contact angle ($b = \sqrt{3}, m_{12} = 0.75$) is 114°, showing a greater extent of spreading ($b = \sqrt{3}, m_{12} = 0$ gives 120°). This suggests that the variable morphology can be described by such a change in the simple model, although whether a wetting transition can be induced by such an external parameter is still undetermined.

From the phenomenological first steps, the mass interaction coefficient must be related

to physically-relevant values. The obvious way to do so is to establish a reference state chosen based on the problem, and relate m_{ij} to it, $m_{ij} = 1 - \frac{|\epsilon_i^\circ - \epsilon_j^\circ|}{\epsilon_i^\circ + \epsilon_j^\circ}$. In addition, an alternative form of the free energy functional itself is being constructed, with additional components that more closely mimic the real system[11].

4 Concluding Remarks

The use of a simple wetting model is not uncommon as an initial extension in studies of cell spreading, and it is promising that altering the effective component interactions does alter the morphology. The benefit of this model is that it is relatively tractable, while maintaining many of the characteristics of the unmanageably complex real system, and is readily extensible to higher levels of complexity (*i.e.* made more physical). It is thus fruitful to consider the system on as simple a level as possible, and incorporate higher levels of complexity systematically.

Within this classical wetting framework, a cell spreading on a surface can be represented as a set of three two-phase interfaces and simulations of slabs containing these interfaces used to determine the interfacial tensions (from the pressure tensor). From these, the analogues to the contact angle and line tension can be calculated via the spreading coefficient. Thus we may also carry out simple simulations that test the added complexity in the model and guide its development.

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